CONTRACT CONCEPT REVIEW

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Title: **Investigative absorption, distribution, metabolism, and excretion (ADME) studies of toxicants in NTP animal model systems**

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I. Purpose

The purpose of this contract is to procure detailed chemical disposition data from a number of studies of selected environmental contaminants or model compounds per year. Such studies are designed to provide both applied knowledge of the fate of chemicals in the intact animal in support of toxicity tests conducted by the NTP and basic knowledge of mechanisms of chemical toxicity. These data will help to predict more accurately the correct doses for compounds to be studied in animal bioassays. Developing fundamental information on chemical structure-activity relationships will permit a more accurate prediction of the fate and toxicity of chemicals that have similar structural or physical properties.

II. Background

This contract is to continue to support chemical disposition studies by providing information on the absorption, tissue distribution, metabolism, and excretion (ADME) of chemicals identified for further study by the NTP. Data from these studies will provide information for the following questions and be used in the design and interpretation of NTP toxicology studies: (1) Does the chemical get beyond the site of application? (2) Where does it go? (3) How is it metabolized by the animal? (4) How and at what rate does it leave the animal?

Most of these studies will be performed in intact laboratory rats and/or mice although some studies may require the use of human and rodent hepatocyte incubations *in vitro* for more accurate extrapolation of results from rodents to humans and for mechanistic studies. This contract will be altered slightly from previous contracts to include ADME studies of chemical disposition in genetically defined strains or genetically-modified animal models that require characterization of chemical disposition (ADME). The work performed under the contract is determined by the needs of the Program. Toxicology studies are designed by a team of NTP scientists and studies such as ADME may be required if there is insufficient information in the literature as determined by Program staff. The chemicals to be studied under the contract are typically not known prior to the award of the contract.

III. Objectives

The overall objective of this NTP contract is to provide detailed information on the ADME/Chemical Disposition of compounds relevant to the mission of the NTP.

The specific objectives are listed below.

- The immediate goal of these studies is to facilitate the design (accurate determination of doses) and interpretation of NTP bioassay studies.
- The long-range goal is to accumulate data to permit a better assessment of structure-activity relationships, and ADME in laboratory animals to facilitate interpretation of the significance of these data to man.
- The contractor shall procure detailed ADME/Chemical Disposition data from a number of studies of selected environmental contaminants or model compounds per year.
- The contractor will provide expertise and capacity to characterize chemical disposition (ADME) in multiple species and genetically defined strains of those species as well as genetically-modified animal models to identify polymorphic genetic loci that influence ADME pathways and toxicity outcomes. Completion of these studies and analysis of the studies for both modeling and quantitative trait analysis and the identification of candidate polyvariant genes will make a significant contribution to toxicology. Determining a genetic and mechanistic basis for these differences between strains is critical. Analysis of data from multiple inbred strains of mice that show significant differences between strains for ADME kinetics may alter the requirements and methods for PBPK modeling and toxicokinetics and toxicodynamics and ultimately offer mechanistic explanations for in vivo toxicity and carcinogenicity results critical for hazard identification and human risk assessment.
- This program incorporates the necessary flexibility to share responsibility with the selected laboratory, the design and analysis of NTP selected chemicals investigated, and acquire expertise and capacity beyond standard requirements of the NTP in order to develop and understand the role of ADME relationships to toxicity and disease.
- The ultimate goal of all these studies is publication in quality peer reviewed journals and NTP peer reviewed technical reports.

IV. Priority

This support contract is considered a high priority because it would support the NIEHS and NTP efforts in assessing the potential health effects of chemical exposures, which will provide scientific information to protect public health.

V. Past Accomplishments

Productivity on Chemical Disposition in Mammals Contract since 1978

1. Approximately 100 Peer Reviewed Publications (recent publications are listed below)

2. Training Activities in Toxicology 11 M.S. degrees; 15 Ph.D. degrees; 16 Postdoctoral Fellows

Kuester, R.K., Sólyom, A.M., Rodriguez, V.P. and Sipes, I.G. (2007) The effects of dose, route and repeated dosing on the disposition and kinetics of tetrabromobisphenol A (TBBPA) in male F-344 rats. Toxicol Sci 96 237-245.

Knudsen, G.A., Jacobs, L. M., Kuester, R.K. and Sipes, I.G. (2007) Absorption, distribution, metabolism & excretion of intravenously and orally administered tetrabromobisphenol A [2,3 dibromopropyl ether] in male Fischer-344 rats. Toxicology 237:158-167.

Kuester, R.K. and Sipes, I.G. (2007) Prediction of metabolic clearance of bisphenol A (4,4'-dihydroxy-2,2-diphenylpropane) using cryopreserved human hepatocytes. Drug Metab Dispos 35: 1910-1915.

Sipes, I.G., Knudsen, G.A. and Kuester, R.K. (2008) The effects of dose and route on the toxicokinetics and disposition of 1-butyl-3-methlimidazolium chloride in male F-344 rats and female B6C3F1 mice. Drug Metab Dispos 36): 284-293.

Hoehle SI, Knudsen GA, Sanders JM, Sipes IG. (2009) Absorption, distribution, metabolism, and excretion of 2,2-bis(bromomethyl)-1,3-propanediol in male Fischer-344 rats. Drug Metab Dispos 37:408-16.

Cheng Y, Wright SH, Hooth MJ, Sipes IG. (2009) Characterization of the disposition and toxicokinetics of N-butylpyridinium chloride in male F-344 rats and female B6C3F1 mice and its transport by organic cation transporter 2. Drug Metab Dispos 37:909-16.